Screening for trisomies at 11–13 weeks' gestation: use of PAPP-A, PlGF or both

A. Mazer Zumaeta[1], A. Wright[2], A. Syngelaki[1], V.A. Maritsa[1], E. Bardani,[1] K.H. Nicolaides[1]

1. Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK.
2. Institute of Health Research, University of Exeter, Exeter, UK.

Correspondence:
Professor KH Nicolaides,
Harris Birthright Research Centre for Fetal Medicine,
Fetal Medicine Research Institute,
King's College Hospital,
Denmark Hill, London SE5 8BB, UK.
email: kypros@fetalmedicine.com

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Contribution

What are the novel findings of this work

1. The performance of screening for trisomies by the first-trimester combined test or the combined test whereby PAPP-A is replaced by PlGF is substantially better at 11 than at 13 weeks' gestation
2. The performance of screening for trisomy 21 during the 11^{th} and 12^{th} gestational week is superior if screening includes PAPP-A rather than PlGF, whereas during the 13^{th} week the performance is slightly higher with the use of PlGF over PAPP-A
3. In our population, with mean gestational age at testing of 12.7 weeks, the performance of screening for trisomies 21, 18 and 13 by maternal age, fetal NT, serum free β-hCG and serum PlGF was similar to that of screening by maternal age, fetal NT, serum free β-hCG and serum PAPP-A.

What are the clinical implications of this work

In first trimester screening for trisomies the preferred biochemical marker is PAPP-A rather than PlGF, especially when biochemical testing is carried out during the 11^{th} week of gestation or earlier. However, if PlGF was to be used rather than PAPP-A the same detection rate can be achieved but at a higher false positive rate. This may be an acceptable compromise to minimize cost and achieve effective screening for both trisomies and preeclampsia.

ABSTRACT

Objective: Serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11-13 weeks' gestation are reduced in pregnancies with fetal trisomies and in those that subsequently develop preeclampsia (PE). In screening for trisomies the established biochemical marker is PAPP-A, whereas in screening for PE the preferred marker is PLGF. The objective of this study is to examine the impact of replacing PAPP-A with PlGF in first-trimester screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency thickness (NT) and free β-human chorionic gonadotropin (hCG).

Methods: This is a prospective screening study in singleton pregnancies for trisomies 21, 18 and 13 by a combination of maternal age, fetal NT and serum PAPP-A and free β-hCG at 11-13 weeks' gestation in which we also measured PlGF. Multiple of the median (MoM) values were calculated for PAPP-A, free β-hCG and PlGF. The data set was randomly split into training and test data sets of roughly equal size and the parameters for PlGF obtained from the training data set were used in risk calculation for the test data set. Standardized detection rates were computed by obtaining the likelihood ratios for biochemistry and fetal NT for trisomy 21, trisomy 18 and trisomy 13 pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific detection rates. These were then weighted according to the maternal age distributions of trisomy 21, trisomy 18 and trisomy 13 pregnancies in England and Wales in 2018. Similarly, standardized false positive rates (FPR) were computed by obtaining the likelihood ratios for biochemistry and NT, as appropriate, in normal pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific FPRs. A modelling approach was used to assess the performance of screening according to gestational age at biochemical testing.

Results: The study population of 71,266 pregnancies, included 70,858 (99.4%) with normal fetal karyotype or birth of a phenotypically normal neonate and 263 with trisomy 21, 109 with trisomy 18 and 36 with trisomy 13. There are five main findings of this study. First, the performance of screening for trisomies by the first-trimester combined test or the combined test whereby PAPP-A is replaced by PLGF is substantially better at 11 than at 13 weeks' gestation; for example, the detection rates of trisomy 21 by the combined test were 94%, 90% and 84%, at 5% FPR, when testing was carried out at 11, 12 and 13 weeks and the respective values in screening by a test whereby PAPP-A is replaced by PLGF were 90%, 87% and 86%. Second, in trisomy 21 pregnancies the deviation of median MoM PAPP-A from normal decreases with increasing gestational age, whereas the deviation in PLGF does not change with gestational age. Third, the performance of screening for trisomy 21 during the 11^{th} and 12^{th} gestational week is superior if screening includes PAPP-A rather than PlGF, whereas during the 13^{th} week the performance is slightly higher with the use of PlGF over PAPP-A. Fourth, in our population with mean gestational age at testing of 12.7 weeks screening by maternal age, fetal NT, serum free β-hCG and serum PAPP-A predicted 88%, 96% and 97% of fetal trisomies 21, 18 and 13, respectively, at FPR of 5%; the respective values in screening by a test whereby PAPP-A

is replaced by PLGF were 85%, 96% and 96%. Fifth, addition of serum PlGF does not improve the prediction of trisomies provided by maternal age, fetal NT and serum free β-hCG and PAPP-A.

Conclusion: In first trimester screening for trisomies the preferred biochemical marker is PAPP-A rather than PlGF, especially when biochemical testing is carried out during the 11^{th} week of gestation or earlier. However, if PlGF was to be used rather than PAPP-A the same detection rate can be achieved but at a higher FPR. This may be an acceptable compromise to minimize cost and achieve effective screening for both trisomies and PE.

INTRODUCTION

Effective first-trimester screening for trisomies 21, 18 and 13 is provided by a combination of maternal age, fetal nuchal translucency (NT) thickness, maternal serum free ß-human chorionic gonadotropin (free ß-hCG) and serum pregnancy associated plasma protein A (PAPP-A); such combined screening identifies about 90% of trisomic fetuses at a false positive rate (FPR) of 5%.[1] Several case control studies reported that in trisomic pregnancies first-trimester maternal serum placental growth factor (PlGF) is reduced and suggested that inclusion of PlGF could potentially improve the performance of combined screening by maternal age, NT, PAPP-A and free β-hCG.[2-8] This issue was also examined in a prospective screening study where serum PlGF, free β-hCG and PAPP-A were measured at 8-13 weeks' gestation and fetal NT at 11-13 weeks in 12,154 normal and 44 trisomy 21 pregnancies; inclusion of serum PlGF was associated with a small improvement in the performance of the first-trimester combined test in screening for trisomy 21.[9]

First-trimester serum PlGF is also useful in screening for preterm preeclampsia (PE); screening by serum PlGF in combination with maternal factors, mean arterial pressure, and uterine artery pulsatility index, at 11-13 weeks' gestation identifies a high-risk group that benefits from the use of prophylactic aspirin.[10-15] Serum PAPP-A can also be used in screening for PE but the performance is lower than with the use of PlGF and if PlGF is used in combination with maternal factors, mean arterial pressure and uterine artery pulsatility index there is no additive value from the use of PAPP-A.[16]

Both serum PAPP-A and PlGF at 11-13 weeks' gestation are reduced in pregnancies with fetal trisomies and in those that subsequently develop PE. In screening for PE the preferred biochemical marker is PLGF, whereas in screening for trisomies the established marker is PAPP-A. The objective of this study is to examine the impact of replacing PAPP-A with PlGF in first-trimester combined screening for trisomies 21, 18 and 13, because such policy could potentially minimize the cost and achieve effective screening for both trisomies and PE.

METHODS

Study population

The data were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first-trimester hospital visit in pregnancy at King's College Hospital and Medway Maritime Hospital, UK. This visit, which is held at 11^{+0} -13^{+6} weeks' gestation, included first, recording of maternal characteristics and medical history, second, ultrasound examination to measure fetal NT thickness as part of screening for trisomies and examination of the fetal anatomy for the diagnosis of major fetal defects, and third, measurement of serum concentration of free β-hCG, PAPP-A and PlGF.[1,17] Serum PlGF was measured by DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA between March 2006 and July 2012 and between August 2013 and March 2017 at King's College Hospital and between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital; it was also measured by Cobas e411, Roche Diagnostics, Penzberg, Germany between August 2012 and July 2012 in both hospitals. Serum free β-hCG and PAPP-A were measured by DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA throughout the whole study period in both hospitals. Gestational age was determined from the fetal crown-rump length.[18] The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

The inclusion criteria for this study were singleton pregnancy undergoing first-trimester combined screening for aneuploidy. We excluded pregnancies ending in termination, miscarriage or stillbirth with no known karyotype and those with abnormal fetal karyotype other than trisomy 21, 18 or 13. The outcomes were divided into first, trisomy 21, 18 or 13 if the karyotype of chorionic villi, amniotic fluid or neonatal blood demonstrated the relevant trisomy, and second, no trisomy 21, 18 or 13 if the karyotype of chorionic villi, amniotic fluid or neonatal blood was normal or the neonate was phenotypically normal.

Statistical analysis

Multiple of the median (MoM) values were calculated for free β-hCG, PAPP-A and PlGF according to the FMF default parameters.[12,20] Diagnostic plots were assessed, and on this basis, further adjustments made for temporal effects, racial origin and gestational age.

To assess the performance of the addition of PlGF to the combined test of maternal age, NT, PAPP-A and free β-hCG for risk calculation for trisomies, the data set was randomly split into training and test data sets of roughly equal size. The purpose of this was to obtain parameters from the training data set, enabling the use of PlGF in risk calculation for the test data set, so that a fair assessment of its performance could be made. Within the training data set, regression models were fitted between $\log_{10}$ PlGF MoM and gestational age for the trisomy 21, trisomy 18 and trisomy 13 pregnancies and correlations between $\log_{10}$ PlGF MoM and $\log_{10}$ PAPP-A MoM and $\log_{10}$ free β-hCG MoM

were calculated for unaffected, trisomy 21, trisomy 18 and trisomy 13 pregnancies. Multivariate Gaussian distributions were obtained for log MoM values for PlGF, PAPP-A and free β-hCG.[19] Likelihood ratios for NT were calculated using the mixture model.[20]

Standardized detection rates were computed by obtaining the likelihood ratios for biochemistry alone or biochemistry and fetal NT for trisomy 21, trisomy 18 and trisomy 13 pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific detection rates. These were then weighted according to the maternal age distributions of trisomy 21, trisomy 18 and trisomy 13 pregnancies in England in 2018.[21] Similarly, standardized FPRs were computed by obtaining the likelihood ratios for biochemistry and NT, as appropriate, in normal pregnancies in the sample and then applying these to each year of maternal age from 12 to 50 to estimate the age-specific FPRs. These were then weighted according to the maternal age distribution of unaffected pregnancies in England in 2018.[21] Confidence intervals (CIs) were obtained by bootstrapping.

We took a modelling approach to assessing the performance of screening according to gestational age at measurement for the combined test and by maternal age, NT, free β-hCG and PlGF. Combinations of MoMs for PAPP-A, free β-hCG and PlGF were simulated from multi-variate Gaussian distributions. Measurements of NT were simulated according to the mixture model.[20] Data were simulated on 10,000 unaffected pregnancies and 10,000 trisomy 21 pregnancies at 11, 12 and 13 weeks. Performance of screening was assessed according to the maternal age distribution in England 2018,[21] as described above, for various false positive rates.

The statistical software package R was used for data analyses.[22]

RESULTS

Study population

During the study period, we examined 74,688 singleton pregnancies. We excluded 3,422 (4.9%) cases because they had missing outcome data (n=2,161), the fetal karyotype was unknown and the pregnancy resulted in termination, miscarriage or stillbirth (n=1,097) or abnormal fetal karyotype other than trisomy 21, 18 or 13 (n=164).

In the study population of 71,266 pregnancies, 70,858 (99.4%) had normal fetal karyotype or birth of a phenotypically normal neonate and 408 (0.6%) had abnormal fetal karyotype, including trisomy 21 (n=263), trisomy 18 (n=109) and trisomy 13 (n=36). Baseline demographic and clinical characteristics of the study population are shown in Table 1. The mean maternal age was 30.8 years (95% CI: 30.53, 30.98) and the mean gestational age was 89.2 days (95% CI: 88.6, 89.9). The expected number of cases of trisomy 21 and trisomies 18 or 13 in our study population, based on the age-related risk for these trisomies, were 265.1 (95% CI, 261.7-268.5), and 142.9 (95% CI, 141.1-144.8), respectively, which is similar to the observed numbers of 263 and 145, respectively.[23,24]

Distributional characteristics of serum PLGF

Distributional characteristics of $\log_{10}$ MoM PLGF in trisomic and non-trisomic pregnancies are given in Table 2. The estimated mean log MoMs given in the table correspond to a constant median MoM of 0.6104 (95% CI: 0.5420 to 0.6876) for trisomy 21, a constant median MoM of 0.5216 (95% CI: 0.4308 to 0.6314) for trisomy 18 and a median MoM of 10^(1.2005-0.01802*gestational age in days) for trisomy 13. Standard deviations of $\log_{10}$ PlGF MoM and correlations between $\log_{10}$ PlGF MoM and $\log_{10}$ PAPP-A and free β-hCG MoM are also provided in Table 2. As is currently the case between biochemical markers and NT in the combined test, PlGF is assumed independent of NT. Figure 1 shows median MoMs in trisomy 21 pregnancies plotted against gestational age for PAPP-A and PlGF; the deviation from normal in the case of PAPP-A decreases with increasing gestational age, whereas the deviation in PLGF does not change with gestational age. In terms of standard deviations, the effect size of trisomy 21 on PAPP-A MoM is larger than it is on PlGF MoM up until just after the beginning of week 13.

Performance of screening

The performance of screening for trisomies 21, 18 and 13 by different combinations of maternal age, fetal NT and maternal serum biochemistry is shown in Table 3. Screening by maternal age, fetal NT and serum free β-hCG and PAPP-A predicted 88%, 96% and 98% of fetal trisomies 21, 18 and 13, respectively, at false positive rate of 5%. Similar results were obtained in screening by maternal age, fetal NT and serum free β-hCG and PlGF. There was no evidence that addition of PlGF improves the performance of screening by maternal age, fetal NT and serum free β-hCG and PAPP-A.

Figure 2 shows the receiver operating characteristic (ROC) curves for prediction of trisomies 21,18 and 13 by maternal age, fetal NT, free-β hCG and different combinations of PAPP-A and PlGF. The area under the ROC curve for trisomy 21 was 0.9580 (95% CI 0.9320-0.9744) in screening by maternal age, fetal NT, free-β hCG and PAPP-A, 0.9542 (95% CI 0.9349-0.9680) in screening by maternal age, fetal NT, free-β hCG and PLGF, and 0.9574 (95% CI 0.9330-0.9731) in screening by maternal age, fetal NT, free-β hCG, PAPP-A and PLGF. The respective values for trisomy 18 were 0.9958 (95% CI 0.9903-0.9982), 0.9744 (95% CI 0.9481-0.9875) and 0.9941 (95% CI 0.9870-0.9973), and for trisomy 13 they were 0.9885 (95% CI 0.9696-0.9957), 0.9833 (95% CI 0.9502-0.9945) and 0.9950 (95% CI 0.9873-0.9979).

The modeled detection rates of trisomy 21 at fixed FPRs of 1-5% in screening at 11, 12 and 13 weeks' gestation are shown in Table 4. During the 11th week, screening with the use of maternal age, NT and free β-hCG, plus PAPP-A was superior to that with use of PLGF, particularly at lower fixed false positive rates. This was also true, but to a lesser degree during the 12th week. During the 13th week detection rates were slightly higher with the use of PlGF over PAPP-A. In order to achieve a detection rate of 90% at 11 weeks, the test falsely screened positive 2.6% of unaffected pregnancies with the use of maternal age, NT and free β-hCG, plus PAPP-A, compared to 5.2% with the use of maternal age, NT and free β-hCG, plus PlGF; the respective values at 12 weeks were 5.5% and 7.7%. At 13 weeks, however, the FPR to achieve 90% detection of trisomy 21 was lower using PlGF than it was using PAPP-A (8.9% vs 10.1%).

DISCUSSION

Main findings of the study

There are five main findings of this study. First, the performance of screening for trisomies by the first-trimester combined test or the combined test whereby PAPP-A is replaced by PLGF is substantially better at 11 than at 13 weeks' gestation. Second, in trisomy 21 pregnancies the deviation of median MoM PAPP-A from normal decreases with increasing gestational age, whereas the deviation in PLGF does not change with gestational age. Third, the performance of screening for trisomy 21 during the 11th and 12th gestational week is superior if screening includes PAPP-A rather than PlGF, whereas during the 13th week the performance is slightly higher with the use of PlGF over PAPP-A. Fourth, in our population with mean gestational age at testing of 12.7 weeks the overall performance of screening for trisomies 21, 18 and 13 by maternal age, fetal NT and serum free β-hCG and PLGF was similar to that of screening by maternal age, fetal NT and serum free β-hCG and PAPP-A. Fifth, addition of serum PlGF does not improve the prediction of trisomies provided by maternal age, fetal NT and serum free β-hCG and PAPP-A.

Comparison with results of previous studies

Our finding of reduced first-trimester serum PlGF in pregnancies with fetal trisomies is consistent with that of several previous case control studies[2-8] and one relatively small screening study.[9] Unlike the suggestion in some of these previous studies that inclusion of PlGF could potentially improve the performance of the first-trimester combined test in screening for trisomy 21, we did not find this to be the case.

We found that in trisomy 21 pregnancies the median PlGF MoM did not change significantly with gestational age between 11 and 14 weeks, which is consistent with results from our previous smaller screening study.[9] Two previous case control studies reported contradictory results; one study found that PlGF MoM in trisomy 21 pregnancies did not change significantly with gestational age between 8 and 13 weeks,[25] but another study found that PLGF MoM decreased with advancing gestational age between 11 and 14 weeks.[4]

We found that the performance of screening by the combined test, or by a test in which PAPP-A is replaced with PlGF, decreases with advancing gestational age between 11 and 14 weeks. This is consistent with the findings of a previous study in which we reported that the detection rates of trisomy 21 by the combined test were 94%, 90% and 83%, at 5% FPR, when testing was carried out at 11, 12 and 13 weeks, respectively; such decreasing detection rate is because the separation in both fetal NT and serum PAPP-A between trisomy 21 and unaffected pregnancies decreases with increasing gestational age.[26]

Implications for clinical practice

The objectives of the 11-13 weeks scan are pregnancy dating, diagnosis of major fetal defects, screening for trisomies and screening for preterm PE. The ability to visualize fetal anatomy is better at 12-13 rather than at 11 weeks, but the performance of screening for trisomies is better at 11 rather than at 12-13 weeks. The best strategy for maximizing both the performance of screening for trisomies and the diagnosis of fetal defects is for biochemical testing and ultrasound scanning to be carried out in two separate visits, with the first done at 10-11 weeks and the second at 12-13 weeks. In such case the combined test with use of PAPP-A would be substantially superior to a test replacing PAPP-A with PlGF; we found that with screening during the 11th week the FPR to achieve detection of 90% of cases of trisomy 21 would be 2.6% with use of PAPP-A and twice as high at 5.2% with PlGF. There is now widespread uptake of cell free DNA testing of maternal blood as an alternative to invasive testing in the investigation of a screen positive result and it could therefore be argued that the benefit from use of PlGF that would be good in screening for PE outweighs the disadvantage of a higher FPR in screening for trisomies. The alternative to two-stage screening is to carry out both biochemical testing and the ultrasound scan in the same visit at 12-13 weeks' gestation, in which case the performance of PlGF is similar to that of PAPP-A, but again the FPR to achieve the same detection rate as at 11 weeks would be substantially higher.

Strengths and limitations

The main strength of the study resides on the prospective examination of a large number of patients providing adequate numbers of affected and unaffected pregnancies for valid conclusions to be drawn on the comparative performance of different methods of screening. The main limitation relates to the dependency of performance on gestational age at screening and this issue has been overcome by modelling that provided separate estimates of performance for the 11th, 12th and 13th week.

Conclusions

In first trimester screening for trisomies the preferred biochemical marker is PAPP-A rather than PlGF, especially when biochemical testing is carried out during the 11th week of gestation or earlier. However, if PlGF was to be used rather than PAPP-A the same detection rate can be achieved but at a higher FPR. This may be an acceptable compromise to minimize cost and achieve effective screening for both trisomies and PE.

Competing interests: The authors report no conflict of interest.

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FIGURE LEGENDS

Figure 1 Median MoMs of PAPP-A and PlGF in trisomy 21 pregnancies plotted against gestational age. The interrupted horizontal line for PAPP-A MoM show the published relationship [19] and the one for PlGF MoM is derived from this study. In terms of standard deviations, the effect size of trisomy 21 on PAPP-A MoM is larger than it is on PlGF MoM up until just after the beginning of week 13.

Figure 2. Receiver operating characteristic curves for prediction of trisomies 21,18 and 13 by maternal age, fetal NT, free-β hCG and PAPP-A (black curve), PlGF (blue curve) or PAPP-A and PlGF (red curve).

Table 1. Maternal and pregnancy characteristics of the study population.

Characteristic	Non-trisomic (n=70,858)	Trisomy 21 (n=263)	Trisomy 18 (n=109)	Trisomy 13 (n=36)
Maternal age (years)	30.7 (30.5, 30.9)	36.7 (32.3, 41.2)	37.0 (30.1, 44.0)	33.8 (22.7, 44.8)
Maternal weight (kg)	70.5 (70.0, 71.1)	69.8 (61.4, 78.3)	70.2 (57.0, 83.3)	69.0 (46.5, 91.6)
Maternal height (cm)	164.6 (163.4, 165.9)	165.2 (145.2, 185.1)	164.9 (133.9, 195.8)	165.5 (111.4, 219.5)
Gestational age (days)	89.2 (88.6, 89.9)	89.7 (78.8, 100.5)	85.2 (69.2, 101.2)	87.4 (58.8, 115.9)
Racial origin				
White	52,411 (74.0)	207 (78.7)	65 (59.6)	30 (83.3)
Black	11,849 (16.7)	34 (12.9)	30 (27.5)	4 (11.1)
South Asian	3,232 (4.6)	8 (3.0)	8 (7.3)	1 (2.8)
East Asian	1,493 (2.1)	11 (4.2)	3 (2.8)	0 (0.0)
Mixed	1,873 (2.6)	3 (1.1)	3 (2.8)	1 (2.8)
Medical history				
Chronic hypertension	960 (1.4)	5 (1.9)	4 (3.7)	1 (2.8)
Diabetes mellitus Type 1	289 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus Type 2	361 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
SLE/APS	156 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Smoker	6,462 (9.1)	20 (7.6)	3 (2.8)	3 (8.3)
Method of conception				
Natural	68,517 (96.7)	242 (92.0)	98 (89.9)	34 (94.4)
In vitro fertilization	1,781 (2.5)	8 (3.0)	5 (4.6)	0 (0.0)
Ovulation drugs	560 (0.8)	13 (4.9)	6 (5.5)	2 (5.6)
Previous trisomy				
Trisomy 21	234 (0.3)	2 (0.8)	1 (0.9)	0 (0.0)
Trisomy 18	91 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Trisomy 13	34 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Data presented as mean (95% confidence interval) or n (%)
SLE = systemic erythematosus lupus; APS = antiphospholipid syndrome.

Table 2. Distributional characteristics of log_{10} MoM placental growth factor values in trisomic and non-trisomic pregnancies.

Parameter		Non-trisomic	Trisomy 21	Trisomy 18	Trisomy 13
Mean	Intercept	0	-0.19278 (-0.21497 to -0.17059)	-0.23445 (-0.27316 to -0.19574)	1.20050 (0.05260 to 2.34841)
	Slope	0	0	0	-0.01802 (-0.03114 to -0.00489)
Standard deviation *		0.16324 (0.16239 to 0.16409)	0.18084 (0.16660 to 0.19778)	0.19046 (0.16810 to 0.21974)	0.15863 (0.12867 to 0.20693)
Correlations					
PAPP-A and PlGF		0.34340 (0.33689 to 0.34988)	0.17316 (0.05332 to 0.28809)	0.33882 (0.16097 to 0.49535)	-0.20928 (-0.50322 to 0.12806)
Free β-hCG and PlGF		0.14692 (0.13971 to 0.15412)	0.03199 (-0.08931 to 0.15236)	0.07988 (-0.10987 to 0.26402)	-0.31757 (-0.58507 to 0.01225)

* Pooled standard deviation 0.16337 (0.16253 to 0.16423)

hCG = human chorionic gonadotropin; PlGF = placental growth factor; PAPP-A = pregnancy associated plasma protein A

Table 3. Estimated detection rates, with 95% confidence intervals, and risk cut-offs for fixed false positive rates between 1% and 5%, in first trimester screening for fetal trisomies 21, 18 and 13 by different combinations of maternal age, fetal nuchal translucency thickness and maternal serum biochemistry. Rates are standardized so that they relate to the maternal age distribution of pregnancies in England and Wales 2018.[21]

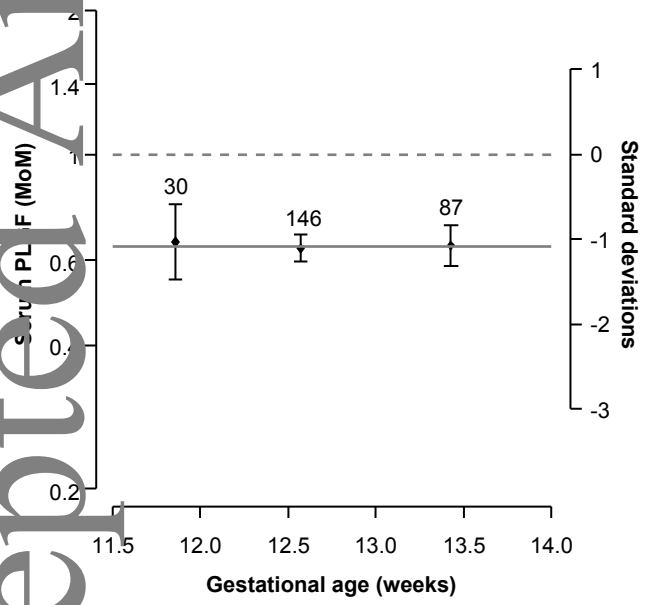
Screening test	False positive rate (%)	Risk cut-off	Detection rate (95% confidence interval)		
			Trisomy 21	Trisomy 18	Trisomy 13
Maternal age + fetal NT	1.0	24.2	65 (57-72)	61 (49-72)	83 (65-100)
	2.0	55.0	73 (66-79)	67 (55-78)	87 (70-100)
	3.0	84.2	77 (71-83)	69 (59-80)	88 (72-100)
	4.0	111.8	79 (74-85)	72 (62-82)	89 (73-100)
	5.0	138.1	81 (76-87)	74 (64-84)	89 (73-100)
Maternal age + serum free β-hCG + serum PAPP-A	1.0	8.5	38 (32-45)	72 (62-82)	55 (36-74)
	2.0	18.7	50 (43-57)	79 (71-88)	69 (53-86)
	3.0	30.1	57 (50-63)	84 (76-91)	78 (64-91)
	4.0	42.1	62 (55-68)	87 (80-93)	82 (71-93)
	5.0	55.0	66 (59-72)	89 (83-95)	86 (76-95)
Maternal age + serum free β-hCG + serum PlGF	1.0	8.8	31 (25-37)	54 (44-64)	48 (27-69)
	2.0	20.1	44 (37-50)	66 (56-76)	60 (40-80)
	3.0	31.8	52 (45-58)	71 (62-80)	67 (48-86)
	4.0	44.3	57 (51-64)	75 (66-84)	70 (52-88)
	5.0	57.1	62 (56-68)	77 (69-86)	74 (57-91)
Maternal age + fetal NT + serum free β-hCG + serum PAPP-A	1.0	15.6	74 (67-81)	88 (81-96)	90 (76-100)
	2.0	39.2	81 (75-87)	92 (85-98)	93 (81-100)
	3.0	68.6	84 (78-90)	93 (88-99)	95 (85-100)
	4.0	101.4	86 (81-92)	95 (90-99)	96 (88-100)
	5.0	137.3	88 (83-93)	96 (92-100)	97 (90-100)
Maternal age + fetal NT + serum free β-hCG + serum PlGF	1.0	15.6	70 (63-77)	82 (73-90)	83 (67-99)
	2.0	39.9	78 (71-84)	89 (83-96)	89 (76-100)
	3.0	69.6	81 (75-87)	92 (87-98)	92 (81-100)
	4.0	102.3	83 (78-89)	94 (89-99)	94 (85-100)
	5.0	137.4	85 (80-91)	96 (91-100)	96 (87-100)
Maternal age + fetal NT + serum free β-hCG + serum PAPP-A +	1.0	11.4	73 (66-80)	86 (78-95)	91 (78-100)
	2.0	33.4	80 (74-86)	91 (84-97)	96 (89-100)
	3.0	63.1	84 (78-90)	93 (88-98)	98 (95-100)

serum PlGF	4.0	99.2	86 (81-92)	95 (91-99)	100 (99-100)
	5.0	140.9	88 (83-93)	96 (93-100)	100 (100-100)

NT = nuchal translucency; hCG = human chorionic gonadotropin; PlGF = placental growth factor; PAPP-A = pregnancy associated plasma protein A.

Table 4. Modeled detection rates of trisomy 21 at fixed false positive rates of 1-5% and false positive rates at fixed detection rate of 90% in screening at 11, 12 and 13 weeks' gestation. Rates are standardized so that they relate to the maternal age distribution of pregnancies in England and Wales 2018.[21]

Method of screening	11.5 weeks		12.5 weeks		13.5 weeks	
	DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)	FPR (%)
Maternal age + fetal NT + serum free β-hCG + serum PAPP-A	81.9	1.0	76.3	1.0	69.4	1.0
	88.1	2.0	82.6	2.0	76.2	2.0
	91.0	3.0	86.0	3.0	80.0	3.0
	92.7	4.0	88.2	4.0	82.5	4.0
	94.0	5.0	89.8	5.0	84.4	5.0
	90.0	2.6	90.0	5.5	90.0	10.1
Maternal age + fetal NT + serum free β-hCG + serum PlGF	73.1	1.0	72.7	1.0	71.1	1.0
	81.5	2.0	79.6	2.0	77.6	2.0
	85.5	3.0	83.1	3.0	81.2	3.0
	88.0	4.0	85.5	4.0	83.7	4.0
	89.8	5.0	86.9	5.0	85.6	5.0
	90.0	5.2	90.0	7.7	90.0	8.9



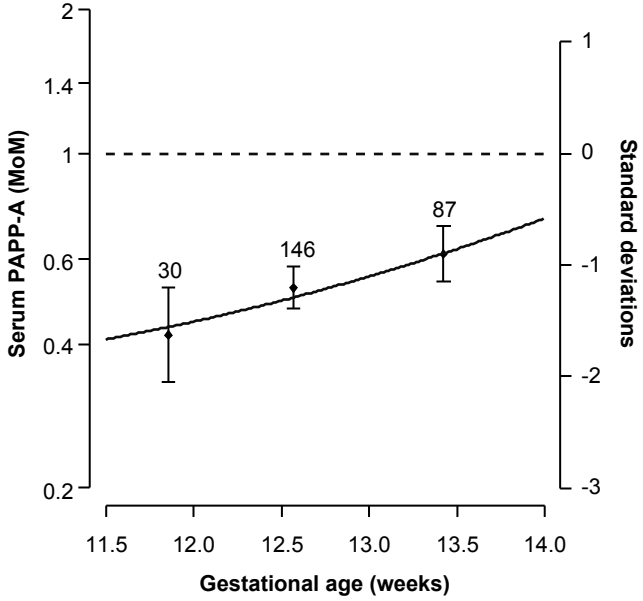


Figure 1

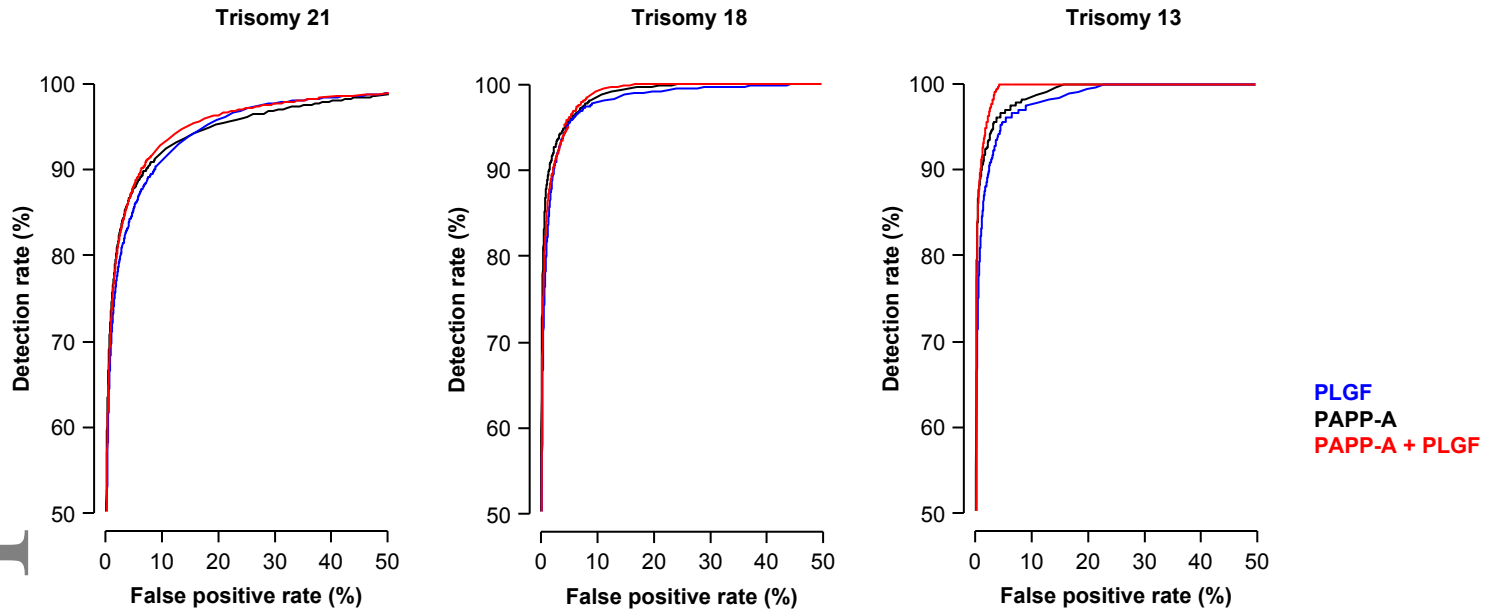


Figure 2